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Metabolism Inspired Electrosynthesis

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Abstract

Drug metabolism is a critical stage in the development of new chemical entities to understand how the drug will behave in the body and to reveal potential toxic metabolites. In this review we discuss how a renaissance in the applications of synthetic electrochemistry can be employed both to identify drug metabolites (and mechanisms) and enable electrosynthetic preparation of drug metabolites for further analysis. Recent advances in electrooxidative drug reactions are reviewed together with a perspective on the future use of electrosynthesis to diversify lead stage drug molecules to enable rapid testing of advanced analogues. A focus on the remarkable advances in the last decade with the inclusion of seminal papers for contextual analysis are reviewed.

1.1 Introduction to drug metabolism

The study of a new chemical entity's (NCE) metabolic profile is a key stage in the pharmacological development of any potentially clinically relevant drug.[1] Failure to elucidate all of the key metabolic processes the NCE undergoes can lead to patient (or unborn child) safety risks, fatalities and market withdrawal of the drug. Metabolism encompasses all of the chemical and redox reactions involved in the biotransformation of a drug within the body.[2]

The ultimate purpose of metabolism is to convert a drug into a more polar form that can be cleared (eliminated) from the body. Clearly a balance needs to be struck between lack of metabolism (drug accumulation), desired metabolism (e.g. pro-drug release) and rapid metabolism (short half-life / duration of action) depending on the drug target. However, it is the generation of toxic or highly reactive metabolites that need to be identified early in the development of a NCE to allow for structural alteration of the drug to maintain the desired activity without the undesired metabolism issues.[3]

Phase I metabolism consists of oxidative, reductive or hydrolytic reactions that either add a polar group or expose a previously masked polar group within the drug. The most common examples being the addition of a hydroxyl group to a C-H bond, reduction of a nitro group to an amine, or hydrolysis of an ester to a carboxylic acid.[4]

Phase II metabolism encompasses reactions upon the revealed or added polar group via conjugation to further increase the polarity of the drug metabolite to enable clearance from the body. Common phase II conjugates include reactions with carbohydrates (glucoronodation), peptides (in particular glutathione), and addition of sulfate groups.

1.2 Metabolic enzymes

There are many classes of enzymes, mainly located within the liver but also the small intestine and the lungs, which are responsible for carrying out these oxidative reactions. In particular the cytochrome p450 (CYP) family of enzymes are responsible for the majority of phase I metabolic events.[5] The CYP class of enzymes are monooxygenases that use an integral haem group to oxidise their substrate. Due to differences in the protein sequence there are numerous CYP isoforms, the major isoforms being 3A4, 3A5, 1A1, 2B6, 2C9 and 2D6. CYP enzymes also exhibit polymorphism which can lead to individual variability regarding the fate and type of drug metabolite formed.[6]

1.3 Biological drug metabolite generation and detection methods

The main methods can be grouped according to whether a whole cell method is used or sub-cellular fractions.[7] Whole cell methods use hepatocytes, liver slices, or isolated perfused liver. Sub-cellular fraction methods include microsomes, cytosolic fraction, S9 fraction, and cDNA expressed recombinant enzymes.[8] These methods have been reviewed comprehensively elsewhere[9] Although they give a snapshot into what may happen to the drug in the body, in almost all cases a preparative quantity of the drug metabolite is not possible. Further insight into drug metabolism provided by any of these means or new complementary methods will dramatically assist drug development.[10] There remains scope for disruptive technologies[11] to give new insight, provide complementary evidence of metabolic pathways, or generate preparative quantities of drug metabolites, and this is where electrochemistry and electrosynthesis could come into its own and the focus of this review.[12]

1.4 Electrochemical generation of drug metabolites

Electrochemical synthesis, the passing of an electrical current through a conductive solution to transform one organic structure into another, is one of the oldest known reaction set-ups.[13] Usually this is performed through the addition or removal of electrons from a substrate directly on the electrode surface (mediated methods also exist) via the application of an electrical potential. Unlike, conventional organic synthesis, the formation of a double layer near the electrode surface, can give rise to exquisite selectivity and control of the reactive radical species formed e.g for *intra* chemical reactions over *inter* for instance.[14] A variety of electrochemical set-ups exist, including undivided, divided and flow cell reactors, each with their own strengths in terms of operational simplicity (undivided) or the ability to deliver enhanced selectivity for one reaction over another (divided or in flow). In this review, there are two major approaches employed: controlled potential and controlled current. Controlled potential reactions require a three-electrode set-up consisting of a working electrode (w.e.) where the desired electroorganic reaction take place, a counter electrode (c.e.) where the balancing electroorganic reaction takes place to preserve the cell circuit (e.g. H_2 formation from a dehydrogenative coupling) and a reference electrode (r.e.), a variety are used in the

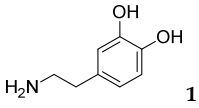
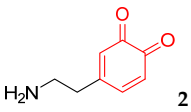
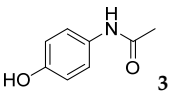
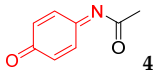
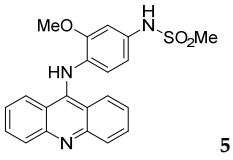
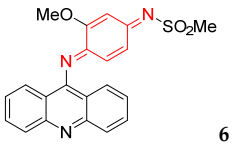
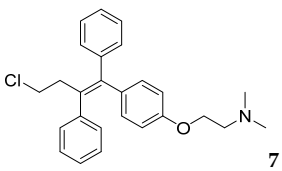
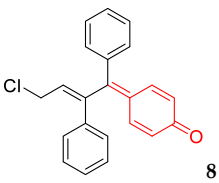
literature including the most commonly encountered for organic reactions: Ag^+/Ag and Fc^+/Fc. The advantage of the controlled potential method is the enhanced selectivity for the desired organic transformation. For instance the cell potential can be held at the desired voltage for the duration of the reaction. One disadvantage of this method is that the cell current can drop to compensate for the increased cell resistance, dramatically extending reaction times.

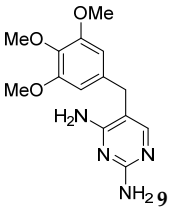
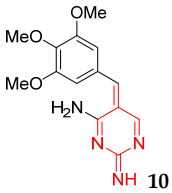
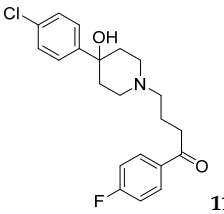
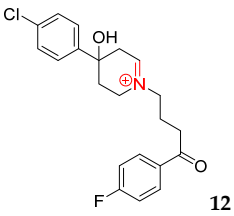
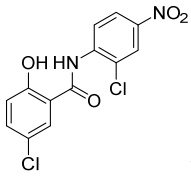
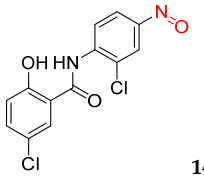
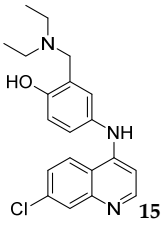
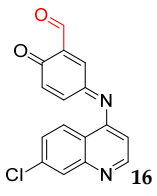
In contrast, the controlled current method requires only a working electrode and a counter electrode. Advantages include the operational simplicity and quick reaction times. A key disadvantage is that the cell potential will fluctuate as the cell resistance changes during the reaction; this can lead to lower selectivity for the desired reaction over time but could be viewed as an advantage for structural diversification.

The use of electrochemical methods to study drug metabolism is much less developed compared to biological methods. However key advantages of electrochemistry, if fully realised for the study of drug metabolism, include: 1) the ability to generate a variety of drug metabolites in a controlled and mild manner; 2) the drugs are studied in a non-cellular environment which simplifies scalability, reproducibility and purification; 3) the ability to gain complementary mechanistic insight into drug metabolism pathways including the use of cyclic voltammetry and spectroelectrochemistry techniques to observe transient metabolites; 4) the ability to synthesise on a preparative scale authentic samples of the desired drug metabolite for toxicity studies. This last point is a key requirement for any new drug molecule and currently would require detection of the drug metabolite via an enzymatic method, elucidation of the structure, and *de novo* synthesis from starting materials which although not insurmountable is a synthetic challenge within complex drug molecules. In this review we showcase the possibilities of directly preparing metabolites from the drug molecule using electrochemistry.

Commonly encountered classes of electrosynthetically generated reactive metabolites that mimic phase I metabolism are summarised in **Table 1**.

Table 1. Commonly encountered electro-metabolism reaction classes.

Entry	Reaction Type	Exemplar conditions	Drug	Product(s)	Reference(s)
			Dopamine (neurotransmitter)		
1	Quinone formation	+150 mV divided cell w.e.= graphite c.e. = graphite ref. = S.C.E pH 7.2 phosphate buffer.	 **1**	 **2**	[15-22]
			Paracetamol (analgesic)		
2	Quinone imine formation	+600 mV Flow cell w.e.= glassy carbon c.e. = Pt wire ref. = Ag/AgCl H_2O:MeOH (9:1) 0.1 M NH_4OAc	 **3**	 **4**	[21], [23-27]
			Amsacrine (antineoplastic)		
3	Quinone diimine formation	+300 mV flow cell w.e.= glassy carbon c.e. = Pd ref. = Pd/H_2 MeCN NH_4CO_2H/NH_4OH pH 7.4	 **5**	 **6**	[28]
			Torimefene (anti-cancer)		
4	Quinone methide formation	100 mV/min scan rate 0 to +2000 mV flow cell w.e. = not stated ref. = Pd/H_2 MeOH NH_4CO_2H pH 7.4	 **7**	 **8**	[26, 29]

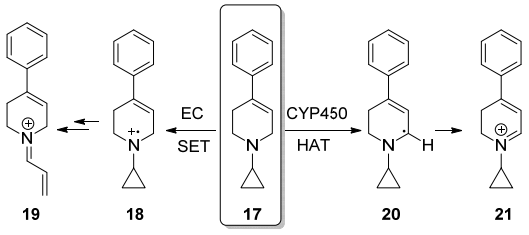
			Trimethoprim (antibiotic)		
5	Imine methide formation	+600mV flow cell w.e.= carbon c.e. = Pt wire ref. = Ag/AgCl 0.1 M phosphate buffer.	 **9**	 **10**	[26]
			Haloperidol (antipsychotic)		
6	Iminium ion formation	0 to +1800 mV Flow reactor w.e.= glassy carbon c.e. = Pd ref. = Pd/H_2 MeCN (aq.) pH range tested	 **11**	 **12**	[22], [27], [30-31]
			Niclosamide (anti-tapeworm)		
7	Nitroso formation	0 to -2500 mV 5 mV/s scan rate flow cell w.e.= boron-doped diamond c.e. = not stated ref. = Pd/H_2 MeOH NH_4OAc	 **13**	 **14**	[32]
			Amodiaquine (antimalarial)		
8	Aldehyde formation	+1000 mV Cell type not stated w.e.= carbon c.e. = Pt wire ref. = Ag/AgCl 0.1 M phosphate buffer.	 **15**	 **16**	[33]

Key: working electrode (w.e); counter electrode (c.e.); and reference electrode (ref.).

The classes of compound in **Table 1** are grouped by structural feature and exemplified with a drug molecule that undergoes electrosynthesis to an oxidised drug molecule detected by mass-spectrometry.[34-36] It is apparent that these successful examples share common features such as quinone and imine formation, highly reactive species, detectable by mass spectrometry but often challenging for preparative synthesis.[37]

On the whole, preparative syntheses were not the main purpose of these studies, as a wealth of analytical and mass-spectrometry fragmentation data was produced leading to structural elucidation of new drug metabolites. Scan rate studies were used to determine the optimal applied voltage for the production of one particular compound over another but in turn this leads to suboptimal reaction conditions such as the use of controlled voltage conditions that are often poorly translated to preparative scale synthesis. However, **Table 1** highlights the power of electrosynthesis to selectively prepare new functionality on drug molecules, an example of late stage functionalisation on complex structures. Furthermore, the reactive nature of these *phase I-like* metabolites, readily allows for trapping via conjugation, for instance with glutathione (GSH), allowing the mimicry of phase II metabolic profiles.[38]

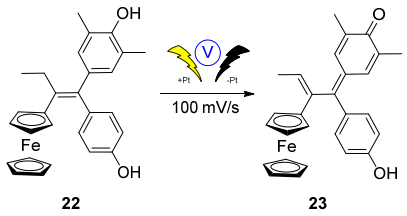
A key caveat to any electrosynthetic metabolism reaction is the potentially different reaction mechanisms to the enzymatic equivalent and lack of a chiral enzymatic environment compared to CYP mediated oxidation. A case in point was demonstrated by Jurva and colleagues (**Scheme 1**).[39]



Scheme 1. Comparison of electrochemical and cytochrome P450 oxidation mechanisms.

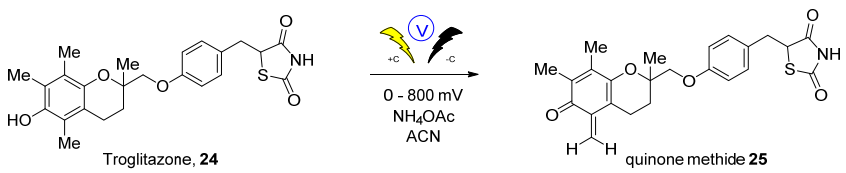
Electrochemical and enzymatic methods can give different products as shown in **Scheme 1**. However, the divergent reaction mechanism between CYP450 oxidation with electrosynthesis can be exploited to give complementary mechanistic insight. Briefly, the electrosynthesis reaction was initiatied via a single electron transfer (SET) to give **18**. As evidence of this a

radical clock experiment was set-up in **17** to demonstrate ring opening of the cyclopropane to give **19**. CYP450 oxidation is a concerted hydrogen atom transfer (HAT) reaction to give **20**, this disparity in reaction mechanism led to no radical clock reaction being observed, instead a reaction outcome with an intact cyclopropane moeity is observed in **21**. This disparity in reaction mechanism can be advantageous as electrosynthesis can be used to probe enzymatic processes and reaction steps.[40]



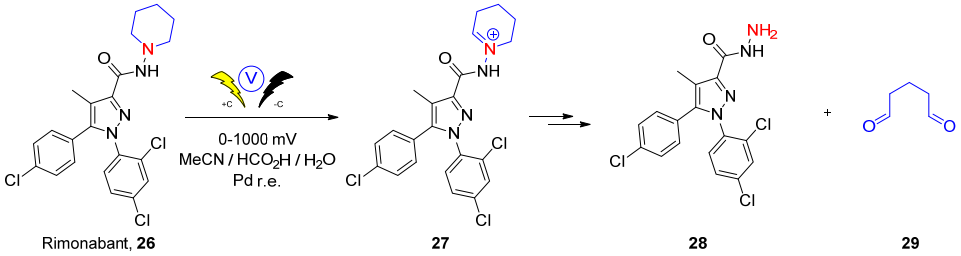
Scheme 2. Example of electrometabolism of an organometallic drug.

A stunning example of this was by Amatore and colleagues[41] who demonstrated that electro-metabolism can be taken one step further by converting a ferrocene containing anti-cancer drug (**22**) to the quinone methide oxidation product (**23**) without affecting the redox cycle of the iron metal centre (**Scheme 2**). Combining complementary information obtained from chemical, biological and electrochemical approaches allowed the identification of intermediates involved in the metabolism of a series of metallo-containing drug molecules. In particular, the use of rapid electrochemical methods (cyclic voltammetry) enabled the monitoring of transient oxidation species over different timescales. Importantly, biological studies confirmed the presence of the electrochemically determined oxidation species in cancerous cells.



Scheme 3. Formation of a quinone methide from Troglitazone.

As a further examples of the general reaction types depicted in **Table 1** and building on research by Madsen;[42] Tahara and co-workers[43] investigated the electrosynthetic behaviour of the anti-diabetes drug, Troglitazone (**24**). Troglitazone was withdrawn from the market because of serious hepatotoxicity in some patient populations thought to be driven via the formation of a highly reactive intermediate in the liver. The authors demonstrated that Troglitazone (**24**) was electrochemically converted to the quinone methide **25** (**Scheme 3**) with a current efficiency of 79% in flow, and approximately 16% of the reaction mixture afforded product **25**. Metabolite **25** was shown to react with *N*-(*t*butoxycarbonyl)-*L*-cysteine methylester to produce a covalent adduct providing clues to the possible hepatotoxicity associated with Troglitazone.



Scheme 4. Electrooxidation of Rimonabant **26**.

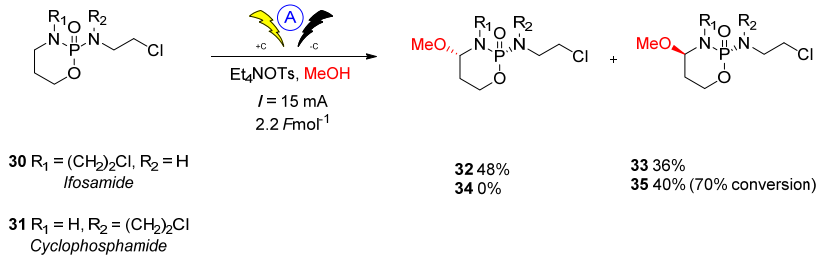
Thorsell and colleagues[44] investigated the electrosynthetic behaviour of the CB1 antagonist, Rimonabant, **26** (**Scheme 4**). Rimonabant was withdrawn from the market due to serious adverse effects in patients, and is well known to give covalent binding to proteins when incubated with HLMs or hepatocytes. A possible mechanism for this is the formation of an aldehyde via CYP450-mediated α-methylene oxidation of the piperidine ring system (**27**). When electrochemically oxidised Rimonabant (**26**) was incubated with a peptide this led to an *N*-terminal amine adduct with a m/z = +64 Da (C_5H_4) originating from cleavage of the piperidine ring system to afford **28**, and highly reactive dialdehyde **29**. Intriguingly, although different mechanisms are in operation between CYP450 and electrochemical methods, there are likely to be similar intermediates via different routes, as the same 64 Da peptide modification was identified when Rimonabant (26) was directly incubated with the peptide.

This electrochemical method was used to identify and provide mechanistic evidence of a previously unknown bioactivation pathway of Rimonabant.

A significant amount of the literature in this area is reliant on fragmentation patterns and predicted chemical reactivity, therefore debate of the proposed structures remains a possibility without authentic samples.[45-48] Therefore, the gold standard would be to preparatively synthesise these electrochemical products.

2. Preparative electrosynthesis of drug metabolites

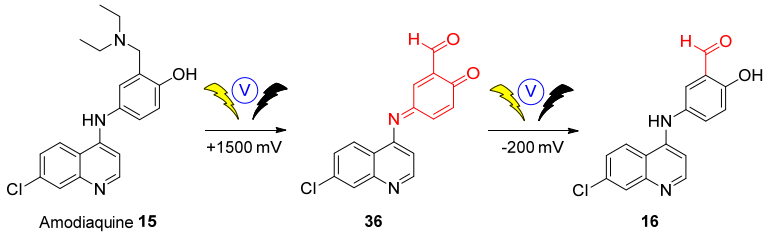
Mass spectrometry directed electrosynthesis has allowed for the possibility of isolating on a preparative scale potential drug metabolites. The inherent advantage of this, despite remaining technological difficulties, is the ability to avoid laborious synthetic development to prepare directly on the drug molecule a single site modification of an NCE to afford oxidative metabolites. This is a key tenet of the concept of late stage functionalisation.[49]



Scheme 5. Electrochemical oxidation of *Ifosamide* and *Cyclophosphamide*.

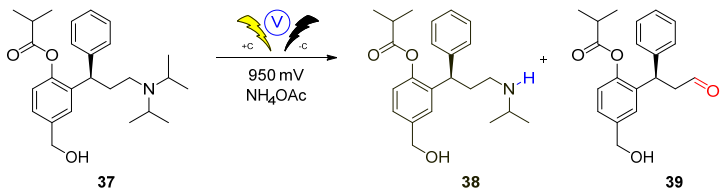
One of the earliest examples of a preparative electrosytnthesis of a drug metabolite was developed by Paci and colleagues for Ifosamide **30** and Cyclophosphamide **31** (**Scheme 5**).[50] These are examples of alkylating anti-cancer agents for use in sarcoma and cerebral tumours that are known to give α-hydroxy metabolites. Using controlled current conditions, the authors developed a route to the analogous α-methoxy metabolites with equipotent activity to the natural α-hydroxy metabolites. Intriguingly, *Ifosamide* gave two stereoisomers, **32** and **33**,

respectively in contrast to the single product for *Cyclophosphamide* which gave **35** only (**34** was not detected).



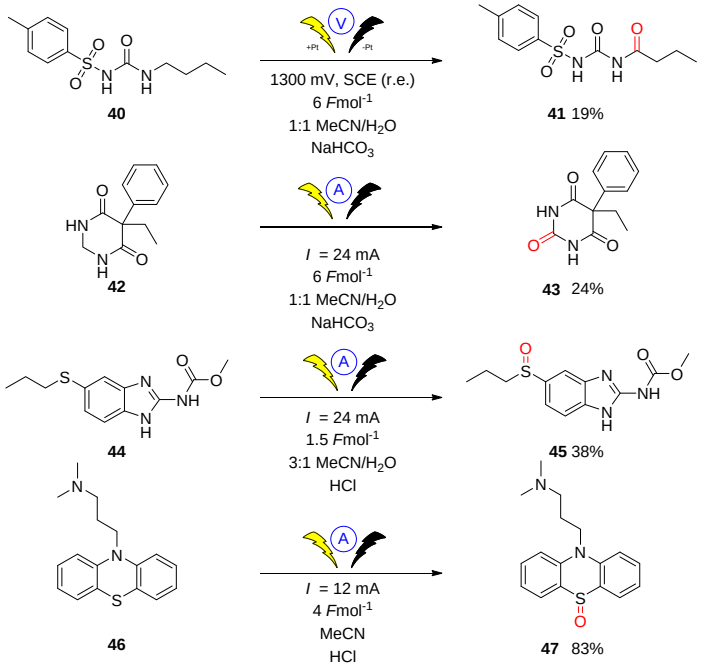
Scheme 6. Preparation of the aldehyde metabolite of Amodiaquine.

An intriguing example of the power of redox cycling the reactivity of the electron oxidant was demonstrated by Johansson and co-workers (**Scheme 6**).[33] Using Amodiaquine (**15**) as the model drug the authors were able to oxidise both the *para*-aminophenol ring system to the quinone imine and the diethylbenzylamine moeity to an aldehyde (**36**) on a preparative scale in flow. By cycling the reaction conditions, the easier to reduce quinone imine ring system was converted back to the *para*-aminophenol unit, leaving an aldehyde moeity as an overall single oxidation event (**16**). The aldehyde **16** was also identified as the major natural metabolite from incubation of **15** with human cytochrome P450 (isoforms CYP1A1 and CYP1B1). Further supporting the rationale that electrochemical systems can mimic metabolic oxidation profiles. The reactive aldehyde in **16** could also be trapped using *N*-acetyl cysteine as a mimic of GSH, *phase II* metabolism.



Scheme 7. Electrochemical oxidation of Fesoterodine.

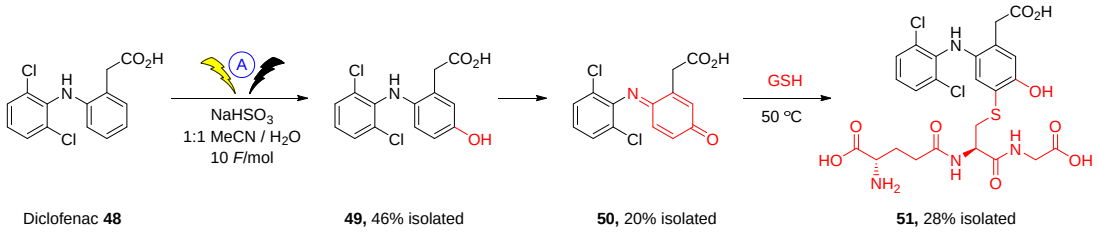
Torres and colleagues at Pfizer developed a bespoke route to the dealkylated metabolites of Fesoterodine **37** as reference compounds for chromatographic study of the degradation of the antimuscarinic drug in biological systems (**Scheme 7**).[51] Two oxidation products **38** (*mono amine dealkylation*) and **39** (*deamination*) were identified. Optimisation of the reaction using scanning cyclic voltammetry led to on a preparative 100 milligram scale, 89% conversion of **37** to dealkylated products **38** and **39** (isolated yields were not stated). A clear advantage of the electrochemical procedure was the clean and fast preparation of metabolites directly from the drug molecule in comparison to traditional bespoke syntheses.



Scheme 8. Selective electro-oxidation of *methylene* and *sulfides* groups on drug molecules.

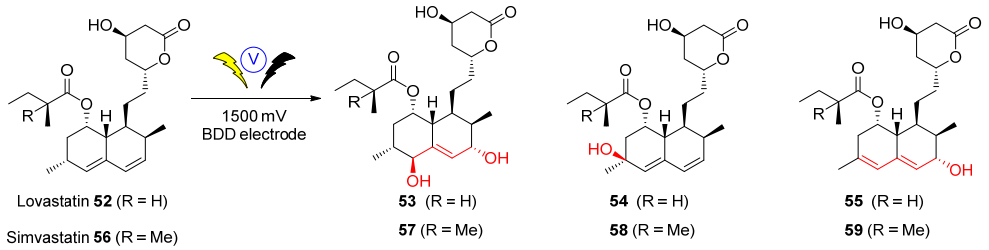
Roth and colleagues have developed two types of prepararative electrosyntheses,[52] selective *S*-oxidation of a thioether to a sulfoxide (no over oxidation to the sulfone was detected) and *peri*-oxidation of the methylene next to an amide or urea to the imide moeity (**Scheme 8**). Using either controlled potential electrosynthesis (preparation of **41**) or controlled current electrosynthesis in flow (preparation of **43**, **45**, and **47**) the oxidised products of tolbutamide **40** (a hypoglycemic medication), primidone **42** (an anticonvulsant medication), albendazole **44** (antihelminthic medication), and chlorpromazine **46** (an antipsychotic medication) were

prepared, respectively. All but one of the oxidation products prepared (compound **41**) are known biological metabolites of the drug precursor. This work therefore holds great promise for a clean late stage electrosynthetic functionalisation of drug metabolites.



Scheme 9. *In situ* GSH trapping of a quinone imine electrooxidation product.

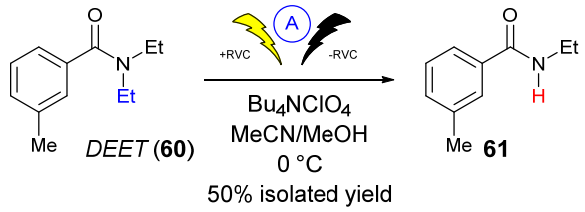
Following on from earlier work with Diclofenac (**48**, NSAID) by Madsen[53] and Faber,[54] Roth and co-workers[52] replicated the diclofenac phase I and II metabolism products on a preparative scale (**Scheme 9**). Using controlled current conditions **48** was converted to the aromatic hydroxylation product **49** in a 46% isolated yield. Further oxidation of **49** afforded quinone **50**, in a 20% isolated yield which could be trapped *in situ* in a 28% isolated yield with glutathione (GSH) to afford **51**. This works shows one of the few examples of electrosynthesis to mimic both *phase I* and *phase II* metabolism on a preparative scale, demonstrating the potential of electrosynthesis both to study and prepare authentic samples of drug metabolites.



Scheme 10. EC/MS preparation of statin drug metabolites.

Khera and colleagues demonstrated the ability to dial-in the desired electosynthetic oxidation state on two commonly prescribed statins (lipid-lowering drugs), *Lovastatin* **52** and *Simvastatin* **56** (**Scheme 10**).[55] Using a coupled electrochemical-mass spectrometry set-up on a milligram

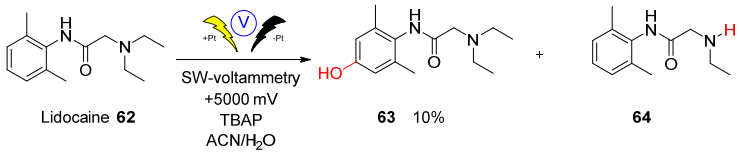
scale, hydroxylated metabolites of both were prepared with comparable conversions to those obtained using CYP BM3 mutants (although the exact yield was not stated).



Scheme 11. An electrochemically driven dealkylation of *DEET*.

Recently, Bal and co-workers[56] demonstrated on a preparative scale a selective *N*-deethylation of the insect repellent, *DEET* (**60**) under controlled current conditions (**Scheme 11**). Comparison with the known human liver microsome metabolites, revealed **61** was the major human metabilite of *DEET*.

The use of electrochemical mediated Fenton conditions (platinum electrode to generate hydroxyl radicals *in situ*) has also begun to find favour as a method to isolate aromatic hydroxylation metabolites.[57] Compared to conventional chemical *Fenton* conditions, there is no longer the requirement to use the Fe^{2+} catalysed decomposition of hydrogen peroxide, as the radicals are generated in a mild and controlled electrochemical cell.[58]



Scheme 12. Lidocaine electrooxidation products.

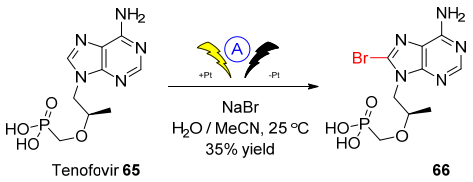
Nouri-Nigjeh and co-workers[59-60] developed an aromatic hydroxylation of Lidocaine (**62**, a local anaesthetic) under electro-Fenton conditions (**Scheme 12**). The authors found that a potential of +5000 mV resulted in low yields of both aromatic hydroxylation (**63**) and dealkylation (**64**) products. Intriguingly, the application of square wave pulse sequences (between 0.2 - 12 s) resulted in a 50-fold selectivity for **63** over **64** in a 10% yield. Similar methods have been applied to paracetamol by the same group.[61] Gul and colleagues have

further optimised the reaction via a design of experiments approach alongside ^{18}O-labelling studies to interrogate the mechanism.[62-63]

There is a growing body of examples of preparative electrosynthesis to drug metabolites. Could this ability to late stage functionalise (LSF) drug molecules be taken one step further and used to develop metabolism inspired electrosynthetic reactions with the goal to generate LSF drug molecules (and metabolites) more generally?

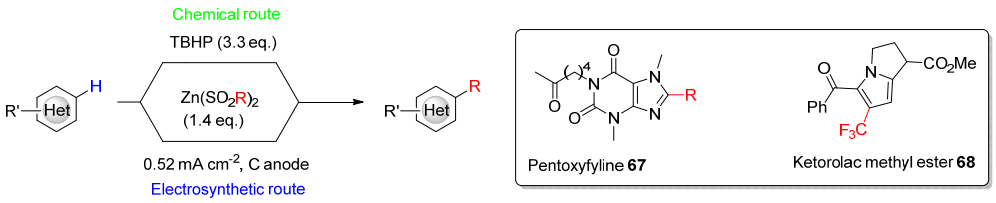
3. Metabolism inspired electrosynthetic methods

Within the expanding field of preparative electrosynthesis drug metabolite production, a new field of more general electrosynthetic methods to late-stage functionalise drug and drug-like molecules is growing.



Scheme 13. Selective C-H bond bromination of the drug Tenofovir (**65**) under electrochemical control (current used not stated).

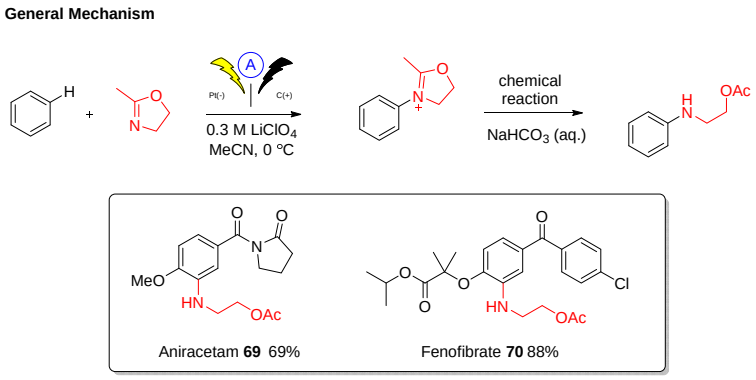
Liu and co-workers at Merck[64] developed an aromatic C-H bromination on a variety of drug molecules (**Scheme 13**). A selective method to achieve this is important as the newly installed C-Br bond can be used as a handle for further selective modifications on an advanced drug molecule including radio-labelling. The method showed wide scope on advanced intermediates and drug molecules including proprietary *Schering* and *Merck* clinical candidates. As a case in point, Tenofovir (a drug used to treat hepatitis B and HIV/AIDS) was directly converted to the desired bromide under mild conditions (neutral pH, controlled current conditions) without the need to protect other complex functionality. A key advantage of the process was the single electrochemical step to **66** (in a 35% yield) versus a five step traditional chemical sequence (20% overall yield).



Method	(67) R = CF_3	(67) R = CF_2H	68
Electrochemical	53%	31%	19%
Chemical	35%	49%	10%

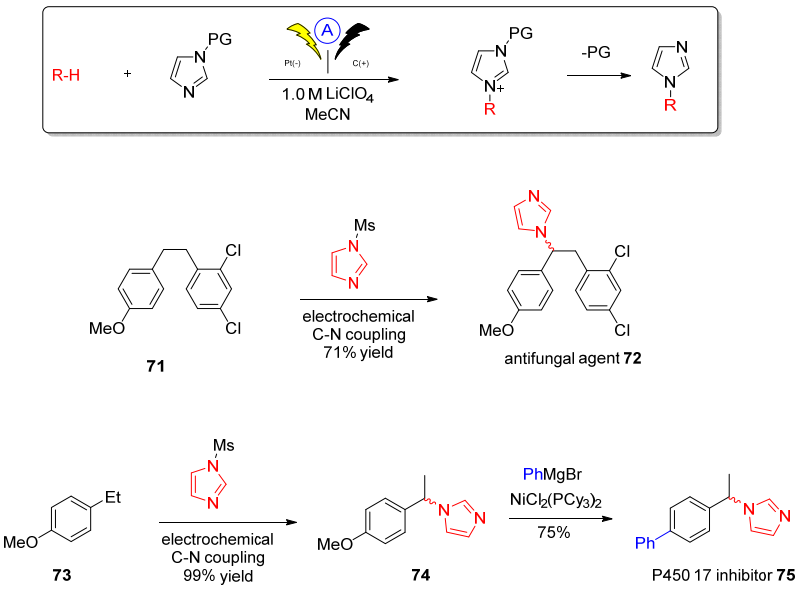
Scheme 14. A radical C-H functionalisation of heteroaryls with fluoromethyl groups under electrochemical control.

Blackmond and co-workers[65] have developed a controllable method to install medicinal chemistry relevant, trifluoromethyl (CF_3) and difluoromethyl (CHF_2) functionality onto drug-like heteroaryl moieties using electrochemistry (**Scheme 14**). Although the majority of the developed chemistry can be achieved using conventional chemical methods eg. a chemical radical initiator (tert-butyl hydroperoxide (TBHP)), this needs to be in significant excess and on the whole the isolated yields were lower than the electrosynthetic method. Of note, was the ability of the reaction to functionalise the drug molecules, Pentoxifyline (used to treat muscle pain) and Ketorolac (a non-steroidal anti-inflammatory analgesic) in a controlled manner which holds promise as a more general late stage method to install fluoromethyl groups into advanced molecules *via* electrochemical C-H bond functionalisation.



Scheme 15. Selective electrooxidative amination of Aniracetam and Fenofibrate.

Yoshida and co-workers[66] have developed a general approach to functionalise heterocycles with formally a primary amine (**Scheme 15**). To achieve this they masked the problematic primary amine, by reacting with a nitrile group to create a cyclic and highly nucleophilic heterocycle. This newly created heterocycle could then intercept an anodically oxidised aromatic partner. The reaction showed good scope and operational ease on 24 examples using a divided cell set-up. Of particular note, was the ability of the reaction to selectively functionalise in high yields complex drug scaffolds, such a Aniracetam (**69**, a prescription drug that modulates the AMPA receptor) and Fenofibrate (**70**, used to reduce cholesterol levels in patients with a high risk of cardiovascular disease) demonstrating the utility of the reaction in late stage functionalisation of drug scaffolds.



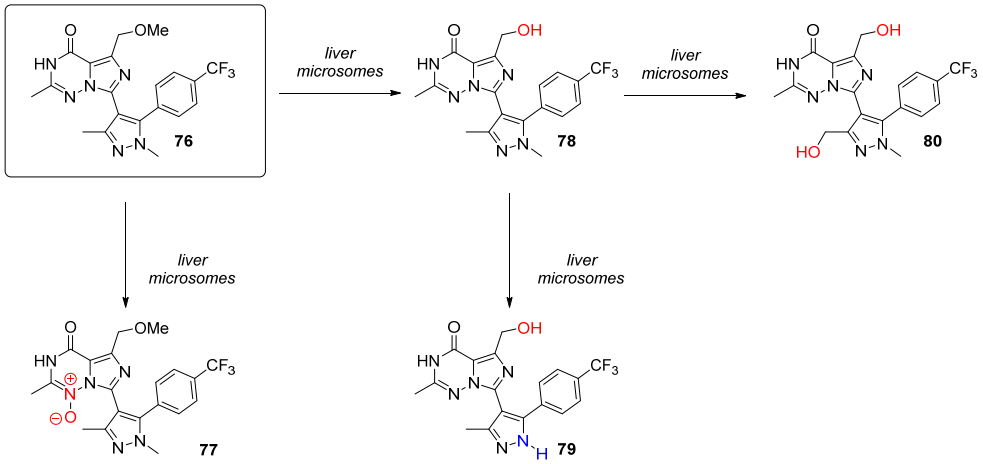
Scheme 16. Anodic oxidation at aryl and benzylic C-H positions to install late-stage imidazole moieties.

Yoshida and colleagues[67] have also developed another divided cell, anodic oxidation method to install imidazoles at both aromatic and benzylic positions (**Scheme 16**). Key to the success of this methodology was the pre-installation of a protecting group such as a mesylate onto the imidazole to prevent over-oxidation during the electrochemical reaction. The reaction showed

good scope with generally high yields on a range of substrates. Of particular importance to the developing field of LSF was its application to cleanly prepare an antifungal agent with selectivity on a double benzylic substrate (**72**) and the near quantitative preparation of a key building block (**74**) towards a reported non-steroidal inhibitor (**75**) of human 17α-hydroxylase-C17, 20-lyase (P450 17).

4. Perspective on future developments

Recent exciting results from Obach and co-workers at Pfizer[68] demonstrated the use of liver microsomes to prepare a diverse array of oxidative products. From a mere nine human phosphodiesterase-2 (PDE2) inhibitors , the reaction afforded thirty six new analogues for evaluation (**Scheme 17**) detected by quantitative cyromicroprobe NMR (qNMR) spectroscopy.



Scheme 17. Treatment of a **76** with liver microsomes yielded new analogues with improved potency.

As might be expected the more polar products had improved metabolic stability, but of significance was the 3-10 fold improvement in potency by introducing these types of functionality on advanced molecules. The authors conclude this is a rapid and cost-effective late-stage lead diversification method for industry.

Electrosynthesis, as a mimic of liver microsomes, could take this one stage further. Electrosynthesis under controlled current conditions could be used to preparing a range of analogues from advanced molecules especially where small quantities are required enabling

rapid late-stage diversification. Advances in *in situ* LCMS and qNMR techniques make this a reality on the horizon. In combination with strides in developing new selective electrosynthetic methodologies that can be applied to drug molecules, this would enable a fully joined-up approach to discovery, detection and generation of drug metabolites, and scalable synthesis of new analogues to expedite drug discovery. To achieve these grand ambitions of metabolism-inspired electrosynthesis, further cutting-edge development of pulse sequences for electrooxidation,[69] engineering advantages for redox cycling and preventing electrode fouling/compound adsorption,[70] microfluidic technologies,[71] and rapid screening technologies[72] are emerging and will all play a role in the wider adoption of electrosynthesis.

Conclusions

Due to the inherent advantages of electrosynthesis such as simpler set up's compared to *in vitro* studies; and mild oxidation conditions compared to chemical synthesis, means the relatively limited number of examples of preparative drug metabolite preparation and methodologies at present will only increase.

Current challenges include selection of electrochemical cells/reactors and the myriad of reaction conditions to be optimised but this can all be overcome. Recent advances in modular electrosynthesis reactors and the more widespread adoption of electrochemistry by the synthetic community will only accelerate the development of new tractable and preparative methods for advanced drug and drug-like molecules. Electrosynthesis has also begun to finding use in preparing *de novo* molecules and drug-like scaffolds for biological evaluation.[73-74] Exciting times certainly lie ahead.

Keywords

electrosynthesis ; diversification; metabolism; oxidation; drug

Acknowledgements

none

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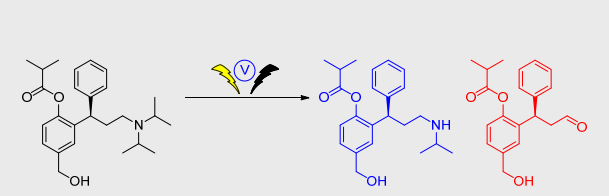

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Metabolism Inspired Electrosynthesis

Recent advances in electro-oxidative drug reactions are reviewed together with a perspective on the future use of electrosynthesis to diversify lead stage drug molecules to enable rapid testing of advanced analogues.